Enhancing hair cell regeneration in mouse and human inner ear

Grant Award Details

Enhancing hair cell regeneration in mouse and human inner ear

Grant Type: New Faculty Physician Scientist

Grant Number: RN3-06529

Project Objective: To enhance the regeneration of sensory hair cells in human and mouse inner ear tissues to restore inner ear function. In this project, hair cell progenitors from human utricles will be characterized for the ability to regenerate ex vivo in the presence of Wnt agonists. In addition, utricles from transgenic mice will be cultured and putative progenitors fate mapped after damage and Wnt treatment. Finally, in vivo mouse models of utricle inner ear hair cell degeneration and regeneration will be characterized.

Investigator:

Name:	Alan Cheng
Institution:	Stanford University
Type:	PI

Disease Focus: Hearing Loss

Human Stem Cell Use: Adult Stem Cell

Award Value: $3,091,595

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Enhancing hair cell regeneration in mouse and human inner ear

Public Abstract: Hearing loss (HL) is a permanent sensory disorder affecting over 278 million people worldwide. In the US and California, 20% of individuals suffer from this sensory deficit. Those affected range from newborns (2 per 1000), to children aged 3-17 (5 per 1000), to adults including the elderly (~33% in aged 65-74 and ~50% >85 years old). Existing treatments aim at improving the symptoms of HL, yet fail to reverse the main underlying pathology, loss of inner ear sensory hair cells (HC). HCs are required for hearing and vestibular function. In the mammalian cochlea, no spontaneous HC regeneration occurs, whereas the vestibular organs exhibit a limited capacity to regenerate HCs. We propose to characterize candidate HC progenitors in vestibular tissues from transgenic mice and surgical patients. The most exciting aspect of this proposal is to understand the natural behavior of HC progenitors in mouse and human inner ear tissues, and whether growth factors enhance regeneration. We will also test whether regenerated HC are functional, and correlate the degree of HC regeneration with functional recovery at the whole animal level, where we can manipulate HC progenitors using transgenic or pharmacologic approaches. Upon completion, we will have learnt whether we can enhance HC regeneration by controlling HC progenitors. Moreover, our model systems may serve as a platform for other basic and preclinical studies aiming at regenerating HC to reverse HL.

Statement of Benefit to California: Hearing loss (HL) is a permanent sensory disorder affecting over 278 million people worldwide. In the US and California, it is estimated that 20% (48 and 7.7 million, respectively) of individuals suffer from this sensory deficit. Those affected range from newborns (2 per 1000), to children aged 3-17 (5 per 1000), to adults including the elderly (~33% in aged 65-74 and ~50% >85 years old). Because normal hearing is essential for language development and communication, the impact of HL is profound. Currently, treatment options including hearing aids and cochlear implantation aim at improving the symptoms of HL, yet fail to reverse the main underlying pathology, loss of inner ear sensory hair cells (HC).

HCs are required for hearing and balance function. Recently, we have defined a population of HC progenitors in the mouse inner ear. Here, we will further characterize these progenitors in human and mouse utricles, the gravity sensing organ, and test if activating developmental signals augments regeneration. If one can direct somatic progenitor cells to replace lost HCs with new functional ones, one can envision therapeutics targeting somatic progenitors in patients with HL. Importantly, our model system will not only provide insights into whether signaling pathways can modulate HC regeneration, but also be used as a platform for pre-clinical drug testing. Successful therapeutics, if safe, can potentially benefit millions of Californians suffering from HL.